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EXAMINER	
GUPTA A	
ART UNIT	**PAPER NUMBER**
1654	24

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

DATE MAILED: 12/04/98

■ This application has been examined ■ Responsive to communication filed on 9-21--98 ■ This action is made final.

A shortened statutory period for response to this action is set to expire 3 Months from the date of this letter.
Failure to respond within the time period will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENTS ARE PART OF THIS ACTION:

1. ■ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ■ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ■ Claims 1-18 and 47-63 are pending in the application.
   Of the above claims, ____ are withdrawn from consideration.
2. ■ Claims 2, 6, 13-16, 48, 52, and 57-62 have been cancelled.
3. ☐ Claims ___ are allowed.
4. ■ Claims 1, 3-5, 7-12, 17-18, 47, 49-51, 53-58, and 63-64 are rejected.
5. ☐ Claims ___ are objected to.
6. ☐ Claims ____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on ____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on ____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on ____ has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under 35 USC 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. ____; filed on ____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

DETAILED ACTION

1. Claims 47, 49-51, 53-58, 63 remain objected to under 37 CFR 1.75 as being a substantial duplicate of claims 1, 2-5, 7-12 and 17 for the reasons set forth in the previous office action. Applicants did not address this issue in their response.

Claim Rejections - 35 USC § 112

2. Claim 58 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In view of applicants amendment, this rejection is withdrawn.

Claim Rejections - 35 USC § 102

3. Claims 1-2, 5-11, 13-14, 17, 47-48, 51-57, 59-60 and 63-64 rejected under 35 U.S.C. 102(e) as being anticipated by Brierley et al.

This rejection is wit drawn.

Claim Rejections - 35 USC § 103

4. Claims 1-18 and 47-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brierley et al. in view of Bussineau et al. (note that Holtz was inadvertently applied in the previous office action).

This rejection is withdrawn.

New Grounds For rejections

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 5, 7-12, 17, 47, 51, 53-57 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brierley et al. in view of Halloran et al.

The claims are drawn to a method of purifying IGF-1 by subjecting to cation exchange chromatography, denaturing and renaturing, hydrophobic chromatography, and reverse phase high performance liquid chromatography, with the proviso that only one cation exchange step is performance in the method.

Brierley et al. teach a method of purification of IGF that comprises a cation exchange step (sulfylpropylated matrix), followed by refolding of the protein with a buffer, followed hydrophobic chromatography (butyl substituted, polymethacrylate matrix), followed by a second cation exchange step (sulfylpropylated matrix) and finally purified by reverse phase chromatography (see claims 1-21). The refolding buffer utilized by the reference comprises 2M urea, 1.5 mM sodium chloride, 15% ethanol, 5 mM sodium borate, .2mM DTT (see col. 6, lines 60-63). The IGF-1 is of a recombinant source and specifically secreted from transformed yeast cells. The IGF-1 is produced in Pichia Pastoris strain (see col. 4, lines 21-40). The difference between the prior art and the instant application is that the reference does not teach the deletion of the second cation exchange step.

However, Halloran et al. teach a method of purifying IGF wherein the steps comprise the use of a cation exchange, followed by hydrophobic interaction chromatography, followed by high performance chromatography, specifically a C8 matrix (see col. 9, lines 20-57). The IGF is produced by a recombinant source including S. cerevisiae and P. Pastoris (see col. 6, lines 27-34). Therefore, since a purification procedure conducting a single cation exchange step yielded a purified IGF product, it would have been obvious that deletion of second cation exchange step from

Brierley et al. would similarly yield a purified product of IGF. One would be motivated to omit the second cation exchange step from the procedure to make the purification procedure less time consuming. It would have been further obvious to use the RP-HPLC for the reverse phase method in Brierley since the reference teach that any reverse phase matrices can be used and Halloran teach the purification of IGF using a C-8 matrix for the RP-HPLC.

6. Claims 1, 5, 7-12, 17, 47, 51, 53-57 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Halloran et al. et al. in view of Brierley et al.

The claims are drawn to a method of purifying IGF-1 by subjecting to cation exchange chromatography, denaturing and renaturing, hydrodphobic chromatography, and reverse phase high performance liquid chromatography, with the proviso that only one cation exchange step is performance in the method.

Halloran et al. teach a method of purifying IGF wherein the steps comprise the use of a cation exchange, followed by hydrophobic interaction chromatography, followed by high performance chromatography, specifically a C8 matrix (see col. 9, lines 20-57). The IGF is produced by a recombinant source including S. cerevisiae and P. Pastoris (see col. 6, lines 27-34). The difference between the prior art and the instant application is that the reference does not teach the denaturing and renaturing step.

However, Brierley et al. teach a method of purification procedure that incorporates a IGF-I unfolding/refolding step, carried out after the cation exchange step (sulfylpropylated matrix) and before a HIC step (butyl substituted, polymethacrylate matrix), that results in higher yield of IGF as compared to a procedure that does not incorporate the unfolding/refolding step (see col. 1, lines 35-46). In a comparison study with a purification procedure that involved cation exchange followed by HIC, the incorporation of the unfolding/refolding step, after the cation exchange and before the HIC, resulted in the yield of 3 times greater the amount of IGF (see col. 11, table III). The refolding buffer utilized by the reference comprises 2M urea, 1.5 mM sodium chloride, 15% ethanol, 5 mM sodium borate, .2mM DTT (see col. 6, lines 60-63). Moreover, the IGF-1 is of a recombinant source and specifically secreted from transformed yeast cells. The IGF-1 is produced in Pichia Pastoris strain (see col. 4, lines 21-40). Therefore, it would have been obvious to incorporate an unfolding/refolding step between the cation exchange and the HIC steps because the incorporation of the unfolding/refolding step would result in higher yield of IGF.

Although Halloran et al. does not teach the use of a particular matrix for the cation exchange and HIC chromatography, it would have been obvious to use those disclosed in Brierley et al. since Halloran et al. states that any suitable matrix for either step is allowable.

7. Claims 1, 3-5, 7-12, 17-18, 47, 49-51, 53-58, and 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Brierley et al. in view of Halloran et al. and in further in view of Bussineau et al. or Halloran et al. et al. in view of Brierley et al. and in further in view of Bussineau et al.

The claims are drawn to a method of purifying IGF-1 by subjecting to cation exchange chromatography, denaturing and renaturing, hydrodphobic chromatography, and reverse phase high performance liquid chromatography, with the proviso that only one cation exchange step is performance in the method.

Brierley et al. in view of Halloran et al. and Halloran et al. et al. in view of Brierley et al. both have been discussed supra and the motivation for their combination has been discussed supra. The difference between the prior art and the instant application is that the reference does not teach the use of the increase in pH to about pH 8 to about pH 12, as claimed in claims 3-5 and 49-50, and does not teach the purification of IGF-II, as claimed in claim 18 and 63.

However, Bussineau et al. teach a method of recombinant production of IGF where in at the end of the fermentation period, an alkaline shock treatment, where an alkali is added to adjust the final pH of the culture medium to the range of 8-11, is conducted. This results in a higher yield of protein from the recombinant production in yeast cells (see page 3-4). Therefore, it would have been obvious to one of ordinary skill in the art to use use an alkaline shock treatment, as outlined in Bussineau et al, to obtain a higher yield in protein.

As to purification of IGF II, as applicant's specification recognizes, the art has recognized the use of yeast cells such as P. Pastoris and S.cerevisiae for the production of IGFs, including IGF II. Therefore, since the source of protein is the same and since IGF II is similar in chemistry to IGF 1, it would have been obvious to one of ordinary skill in the art that the method outlined in Brierley et al. would be applicable to IGF II.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of

time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can normally be reached on (703) 308-0254. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Anish Gupta

Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600